REMARKS

The Claim Amendments

Claims 1, 5, 15-18, 20, 29, 32 and 36-39 are currently pending. Claims 5 and 29 have been canceled with this response. Claims 16, 18 and 36-39 have been amended merely to correct matters of form. Claim 1 has been amended to recite that each strand of the siRNA molecule is 18 to 27 nucleotides in length and also that about 100 percent of the nucleotide positions in one or both strands of the siRNA molecule are chemically modified and the antisense strand of the siRNA molecule comprises about 5, 6, 7, 8, 9, 10 or more 2'-O-methyl nucleotides. Support for the amendment to claim 1 can be found at, *inter alia*, pages 11 and 12 (18 to 27 nucleotides); page 13 (about 100% modified); and pages 19 and 27-29 (about 5-10 or more 2'-O-methyl nucleotides). Support is also found in USSN 60/358,580 at page 11, last paragraph and in USSN 60/363,124 at page 12, first full paragraph, both of which are incorporated by reference.

Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

The Sequence Listing

Applicants have enclosed a new sequence listing and request its entry in place of the previously entered sequence listing. The sequence listing adds SEQ ID NO:1706. The sequence represents GenBank entry D11168 (see Table I). The version of D11168 appearing in the sequence listing as SEQ ID NO: 1706 appeared in GenBank on February 2, 2000. Applicant submits that the CD-R submitted in lieu of the paper copy and the CD-R submitted for the computer-readable copy are identical in content. The sequence listing adds no new matter and applicants respectfully request its entry.

Priority

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The Office has determined the effective filing date of the claims to be that of application 60/401,104, which has an effective filing date of August 5, 2002. The Office alleges that Applicant is not entitled to an earlier effective filing date because it has not complied with one or more conditions for receiving the benefit of an earlier filing date. In particular, the Office argues that the instant application is not entitled to the filing date of 60/363,124 because it alleges that PCT/US03/05043 does not claim the benefit of 60/363,124 and 60/358,580 in the continuity data.

Applicant respectfully points out that the Office is in error with respect to the priority claim. Contrary to the Office's allegation, PCT/US03/05043 does, in fact, claim the benefit of 60/363,124 and 60/358,580 in the continuity data. Applicant has attached herewith a copy of the application data sheet filed with the instant application, as well as a copy of the filing receipt received from the USPTO for the instant application. In addition, Applicant has attached herewith a copy of the PCT Request filed with the PCT/US03/05043 application. The PCT Request shows that PCT/US03/05043 claims the benefit of 60/363,124 and 60/358,580. The Application data sheet and the filing receipt for the instant application show that PCT/US03/05043 claims the benefit of 60/363,124 and 60/358,580 in the continuity data.

The claims presented above all find support in, *inter alia*, the '124 application. In particular, amended claim 1 finds support for the antisense strand having between 18-27 nucleotides complementary to HCV RNA at p. 18, lines 1-5, p. 12, line 6, p. 425, entry in Table III for GenBank Accession No. NM_000594; and 2'-deoxy-2'-fluoro pyrimidine modifications at p. 6, line 19 to page 7, line 18 (where R3 of Formula II is F); page 10, lines 11-16 and 25-30; and page 11, lines 6-11 and 20-25.

Support for the dependent claims can also be found in, *inter alia*, the '124 application:

Claim	Support
36	One or more pyrimidine nucleotides present in sense strand are 2'-O-methyl pyrimidine nucleotides: p. 10, lines 13, 27, p. 11, lines 8, 22
37	One or more purine nucleotides present in the sense strand are 2'-deoxy purine nucleotides: p. 6, lines 14-15
15	One or more pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides: p. 10, lines 13-14, 27, p. 11, lines 8-9, 22

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Claim	Support
16	Sense strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand: p. 10, lines 6-7, 20-21, p. 40, lines 1-18
17	Terminal cap moiety is inverted deoxy abasic moiety: p. 5, line 16, p. 14, lines 10-13, p. 40, lines 4-18.
18	One or more pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides: p. 10, lines 13-14, 27, p. 11, lines 8-9, 22
39	One or more purine nucleotides present in the antisense strand are 2'-deoxy purine nucleotides: p. 6, lines 14-15
32	Composition comprising the siRNA molecule in a pharmaceutically acceptable carrier or diluent: p. 18, lines 15-19

Therefore, the instant application is entitled to a priority date of at least March 11, 2002.

Claim Objections

Claim 5 has been objected to under 37 CFR 1.75(c) as being of improper dependent form for failing to further limit the subject matter of the previous claim. Claim 5 has been canceled, rendering the objection moot. Applicant respectfully requests withdrawal of the objection.

35 U.S.C. §103(a) Rejections

Claims 1, 5, 15-18, 20, 29, 32, and 36-39 stand rejected under 35 USC §103(a) as allegedly obvious over Wu *et al.*, in view of Elbashir *et al.,* Pavco *et al.,* Hammond *et al.*, Caplen *et al.,* and Parrish *et al.* Claims 5 and 29 have been canceled. As such, the rejection is moot as applied to these claims. Applicants respectfully traverse the rejection as it applies to claims 1, 15-18, 20, 32 and 36-39.

The Office relies on Wu et al. for its teaching of targeting HCV with antisense oligonucleotides. As acknowledged by the Office, Wu et al does not teach siRNA duplexes or chemical modifications, including 2'-O-methyl modifications. The Office relies on Hammond and Caplen for their general teachings regarding siRNA and RNAi, and relies on Elbashir, Parrish, and Pavco for their teachings relating to chemical modifications of siRNA or antisense and ribozymes. The Office argues that it would have been obvious to substitute a siRNA duplex, as taught by Elbashir and Parrish, for

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the antisense oligonucleotide taught by Wu et al. The Office further argues that it would have been obvious to incorporate 2'-O-methyl, 2'-deoxy, and 5'-phosphates, as taught by Elabshir, as well as 2'-deoxy-2'-fluoro modifications, as taught by Parrish into a siRNA duplex specific for HCV. Finally, the Office argues that it would have been obvious to incorporate inverted abasic deoxyribose, as taught by Pavco, into the siRNA duplex.

However, none of these references, alone or in combination, make obvious the presently claimed siRNA constructs in which about 100 percent of the nucleotide positions in one or both strands of the siRNA molecule are chemically modified and the antisense strand of the siRNA molecule comprises about 5, 6, 7, 8, 9, 10 or more 2'-O-methyl nucleotides.

The Office focuses its argument on enhanced delivery of chemically modified oligonucleotides in general, arguing that one would have a reasonable expectation that the instantly claimed siRNA molecules would successfully inhibit HCV because chemical modifications were known in the art to enhance the delivery of oligonucleotides. However, the Office makes no mention whatsoever of the activity of chemically modified siRNA molecules targeted to HCV. Further, none of the cited art, alone or in combination, provides any insight into whether highly modified double-stranded siRNA nucleic acid constructs, such as the claimed siRNA constructs, would function once delivered. Indeed, Parrish and Elbashir teach away from highly modified siRNA constructs. Parrish expressly teaches that modifications of the antisense strand decrease RNAi activity (see pages 1081 and 1082, Figures 5 and 6). Elbashir teaches that extensive substitution with 2'-deoxy or 2'-*O*-methyl modifications abolishes RNAi. In a section tellingly entitled, "The siRNA User Guide," Elbashir expressly teaches away from highly modified siRNA constructs:

> "The siRNA User Guide"
>
> Efficiently silencing siRNA duplexes are composed of 21 nt sense and 21 nt antisense siRNAs and must be selected to form a 19 bp double helix with 2 nt 3'-overhanging ends. 2'-deoxy substitutions of the 2 nt 3' overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNAse resistance of siRNA duplexes. **More extensive 2'-deoxy or 2'-*O*-methyl modifications, reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNAP assembly.**

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(*see*, page 6885, left col.; emphasis added; see also, Tuschl et al. US Pat. Publ. 2004/0259247, paragraphs [0178] to [0179]). Because the only teaching in the cited art addressing the issue of the degree of modifications tolerated in siRNA molecules expressly states that more than a few end modifications should be avoided, it could not have been obvious to make the highly modified constructs now being claimed with a reasonable expectation of success. The present claims go directly against the express teachings of the art. Consequently, the present claims cannot be obvious over the cited art.

Claims 1, 5, 15-18, 20, 29, 32, and 36-39 stand rejected under 35 USC §103(a) as allegedly obvious over McCaffrey et al., in view of Elbashir et al., Pavco et al., Caplen et al., and Parrish et al. Claims 5 and 29 have been canceled. As such, the rejection is moot as applied to these claims. Applicants respectfully traverse the rejection as it applies to claims 1, 15-18, 20, 32, and 36-39.

The Office relies on McCaffrey et al. for its teaching of siRNA mediated inhibition of HCV expression with 21-nucleotide siRNAs. The Office acknowledges that McCaffrey et al. do not teach chemical modifications. The Office relies on the teachings of Parrish, Elbashir, Pavco, and Caplen as described above. The Office argues that it would have been obvious to incorporate 2'-O-methyl, 2'-deoxy, and 5'-phosphates, as taught by Elabshir, as well as 2'-deoxy-2'-fluoro modifications, as taught by Parrish, as well as phosphothioates and inverted abasic deoxyriboses, as taught by Pavco, into the siRNA duplex taught by McCAffrey.

Again, the Office focuses its argument on enhanced delivery of chemically modified oligonucleotides in general and makes no mention whatsoever of the activity of chemically modified siRNA molecules targeted to HCV. As discussed above, none of the cited art, alone or in combination, provides any insight into whether highly modified double-stranded siRNA nucleic acid constructs, such as the claimed siRNA constructs, would function once delivered. Indeed, Parrish and Elbashir teach away from highly modified siRNA constructs. Because the only teaching in the cited art addressing the issue of the degree of modifications tolerated in siRNA molecules expressly states that more than a few end modifications should be avoided, it could not have been obvious to

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make the highly modified constructs now being claimed with a reasonable expectation of success.

Thus, none of the cited references, alone or in combination, make obvious the presently claimed siRNA constructs in which about 100 percent of the nucleotide positions in one or both strands of the siRNA molecule are chemically modified and the antisense strand of the siRNA molecule comprises about 5, 6, 7, 8, 9, 10 or more 2'-O-methyl nucleotides. Consequently, the present claims cannot be obvious over the cited art.

Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,

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